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Hyper- and hypo-mentalizing in patients with first-episode schizophrenia: fMRI and behavioural studies

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Abstract

Background: Historically, research investigating neural correlates of mentalizing deficits in schizophrenia has focused on patients who have been ill for several years with lengthy exposure to medication. Little is known about the neural and behavioural presentations of theory-of-mind deficits in schizophrenia, shortly after the first episode of psychosis.

Methods: We investigated social cognition in seventeen recently diagnosed first-episode schizophrenia (FES) patients with little or no exposure to antipsychotic medication and 1:1 matched healthy controls. We recorded behavioural and neural responses to the Animated Triangles Task (ATT), which is a non-verbal validated mentalizing task that measures the ascription of intentionality to the movements of objects.

Results: FES patients under-interpreted social cues and over-interpreted non-social cues. These effects were influenced by current intelligence (IQ). Control group and FES neural responses replicated earlier findings in healthy adults. However, a region of anterior medial prefrontal cortex (amPFC) of FES patients showed a different response pattern to that of controls. Unlike healthy controls, patients increased activity in this social cognition region while studying ‘random’ movements of shapes, as compared to the study of movements normally interpreted as ‘intentional’.

Conclusions: Mentalizing deficits in FES consists of hypo- and hyper-mentalizing. The neural pattern of FES patients is consistent with deficits in the ability to switch off mentalizing processes in potentially social contexts, instead increasing them when intentionality is not forthcoming. Overall, results

demonstrate complexities of theory of mind deficits in schizophrenia that should be considered when offering social cognitive training programs.

1. Introduction

During recent years there has been an increased focus on social cognitive deficits as core deficits in schizophrenia with a considerable impact on functional outcome¹⁻³. Specifically, theory of mind (ToM), social perception, social knowledge, attributional bias, and emotional processing have all been recognized as domains of particular interest in schizophrenia^{4, 5}. In a meta-analysis of these social cognitive domains in schizophrenia, Savla et al.⁶ concluded that theory of mind and social perception were the domains most severely affected.

Yet, patients with schizophrenia are a heterogeneous group and many speculations have been made regarding possible social cognitive subgroups^{2, 7-9}. In this paper, we refer to ‘mentalizing’, the act of inferring the mental states of others, which enables us to predict their actions¹⁰. It has been suggested that one subgroup of patients perform poorly in social cognitive tests due to reduced ToM abilities (hypo-mentalizing) as seen in patients with autism, while another subgroup of patients perform poorly due to social interpretation of non-social events (hyper-mentalizing). The latter group has been associated with paranoia while the former group has been associated with negative symptoms^{11, 12}. It has also been suggested that patients may in fact be hypo-mentalizing and hyper-mentalizing at the same time¹³⁻¹⁵. E.g. a paranoid patient can over-interpret a neutral, casual interaction like people randomly passing by on the street as

“evidence” of being persecuted by the government. At the same time, the patient can perceive only the literal meaning of a spoken dialogue and overlook sarcasm. This complexity is yet to be resolved.

In earlier literature, many brain regions have been consistently associated with various aspects of social cognition. These include anterior medial prefrontal cortex (amPFC), the temporoparietal junction (TPJ), temporal poles, the precuneus, dorsal anterior cingulate cortex (dACC), posterior superior temporal sulcus (pSTS), superior temporal gyrus (STG), inferior frontal gyrus (IFG), amygdala, fusiform face area (FFA), inferior parietal lobule (IPL), premotor cortex, anterior hippocampus, dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC) ^{16, 17}.

More specifically, attribution of other people’s mental states, ToM, has been associated with a specific neural network of brain regions: the posterior superior temporal sulcus (pSTS), the left and right temporoparietal junction (TPJ), the temporal poles, the precuneus (PC), and the medial prefrontal cortex (mPFC) ¹⁶⁻¹⁹.

Recently, Schilbach and colleagues²⁰ used a meta-analytically defined mentalizing network in a hypothesis-driven manner in order to compare functional connectivity in patients with schizophrenia and age- and gender matched healthy controls based on MRI data. The researchers found indications of decreased functional connectivity between regions involved in mentalizing in schizophrenia patients. However, they found no significant associations between connectivity and symptoms, duration of illness, and chlorpromazine-equivalents.

Literature reviews of fMRI studies have also identified deficits within the mentalizing networks in schizophrenia^{21, 22}.

Many different fMRI paradigms have been used to measure ToM. In this study, we chose to use the Animated Triangles Task (ATT) which is a well validated non-verbal ToM paradigm^{18, 23, 24}. In the ATT, subjects are shown small film clips of two triangles moving either in a random way or interacting with apparent intentionality.

The classic version of AT, which we used in this study, has been used previously to investigate ToM brain activity in schizophrenia. For example, Das et al.²⁵ found that compared to the healthy control subjects, male patients with schizophrenia had a reduced neural activity in the right superior temporal gyrus (STG), temporoparietal junction (TPJ), and inferior frontal gyri (IFG). The authors suggested that this reduction of activity could reflect an impairment of reasoning about mental states of others, or ‘mentalizing’²⁶. In a similar vein, Koelkebeck et al.²⁷ did voxel-based morphometry analysis based on MRI scans. They found that in patients with schizophrenia, ToM deficits from the behavioral responses to the ATT correlated with grey matter volume reductions in pSTS and mPFC.

In a recent study, Martin et al.²⁸ identified a common network in patients with schizophrenia and healthy controls that separate the viewing of intentional and random ATT animations. However, behavioral data showed that patients performed worse on the ToM tasks compared to the controls. It was concluded that mentalizing deficits in schizophrenia may be due to inefficient connections within these social brain networks²⁸.

All studies thus far of ToM deficits on the ATT have been conducted on patients with lengthy exposure to medication. However, first episode patients show differences in cognitive abilities compared to long-term patients^{13, 29}, that could reflect long-term medication effects and/or the progression of the disorder.

In this study, we examined the neural basis of ToM impairments in recently diagnosed patients with first episode schizophrenia (FES) receiving no or sparse antipsychotic medication. The patients had not been medicated for more than a maximum of 6 weeks over their lifetime, and had not been stigmatized by a diagnosis of schizophrenia. If ToM deficits are present early in the course of the disorder, we should be able to detect them at this early stage. Neural correlates would provide insight into how those deficits materialize. Our prediction, based on a recent meta-analysis of the ATT in patients with autism and schizophrenia¹³, was that variability of performance on ToM tasks in FES are due to deficits of appropriate neural responses to social (hypo-mentalizing) and non-social (hyper-mentalizing) stimuli.

2. Methods and Materials

Subject Recruitment

Patients were recruited from OPUS, Clinic for people with schizophrenia, which is an intensive 2-year early-intervention program consisting of assertive community treatment, cognitive behavioral therapy, psychoeducational family treatment, and social skills training^{30, 31}. Patients were recruited and tested a few days after receiving a diagnosis of schizophrenia and

being included in OPUS, except for one patient who had been included for 403 days but never received any medication. Healthy control subjects were recruited via advertisements in four local newspapers.

Patients

Patients with first episode schizophrenia were included in the study if they met the ICD-10 (International Classification of Disease 10th edition, WHO) criteria for schizophrenia; had no neurological disorder or severe head trauma according to ICD-10; or an ICD-10 diagnosis of drug- or alcohol dependency. Patients were excluded if they had an estimated premorbid IQ<70 based on previous history or if they were not able to understand spoken Danish sufficiently to comprehend testing procedures. Patients had received less than 6 weeks of lifetime pharmacological treatment prior to the diagnostic interview. In all, twenty-three patients between the ages 18-30 years were included. Four patients were unable to complete the fMRI scans due to worsening of their psychotic symptoms caused by scanner noise. Two patients stopped the scan midway. The seventeen patients included in the fMRI analysis had the following medication histories: eight patients were antipsychotic-naïve; nine patients had been medicated with a low dose of atypical antipsychotics for less than 6 weeks; four patients had been medicated for less than 6 weeks with an antidepressant (1 without an antipsychotic), three received hypnotics (2 in combination with an antipsychotic).

Healthy control subjects

Healthy control subjects were matched one-to-one to patients on age, gender, handedness, educational level (based on the patients' last commenced educational level), community of residence and parental socio economic status based on the highest parental education and expected parental income according to Statistics Denmark regarding wages (www.dst.dk/en). Healthy control subjects were excluded if they had a history of mental illness (self or among first-degree relatives), had psychotic symptoms, had a history of severe head injury or neurological illness (meeting ICD 10 criteria), or an ICD-10 diagnosis of drug- or alcohol dependency. Nineteen healthy control subjects were included, however, one was excluded due to scanner problems, and one was excluded because the matched patient did not complete the session. This left 17 control subjects in the analysis, paired with 17 patients.

Ethics

All participants in this study received written and verbal information about the project and a written informed consent was obtained before inclusion. The study was approved by The Central Denmark Region Committee on Health Research Ethics (Ref: M- 2009-0035) and the Danish Data Protection Agency. The project complied with the Helsinki-II-declaration.

Procedure

The patients underwent neuropsychological testing and were scanned with fMRI by VB a few days after the OPUS inclusion. Patients performed the ATT twice, once outside the scanner and once inside the scanner.

Seven of the patients were psychologically tested (outside the scanner) at home and ten were tested at VB's office at Aarhus University Hospital Risskov.

Intelligence

Premorbid intelligence was estimated using DART (Danish Adult Reading Test), which is a Danish version of NART (The Nelson Adult Reading Test)³². The test consists of 50 rare words, which the subjects are asked to read aloud, and the number of correct pronunciations are scored. The NART has been shown to be a valid and reliable estimation of premorbid intelligence in schizophrenia^{33, 34}. Estimation of current intelligence was done using four sub-tests from WAIS-III (Wechsler Adult Intelligence Scale, Third edition)³⁵. The four sub-tests were chosen based on high correlation with the total WAIS-III IQ-score: Matrix Reasoning, Block Design, Vocabulary, Similarities³⁶.

Psychopathology, Clinical Measures and Drug Screening

At inclusion to the OPUS Clinic all FES patients were interviewed with the PSE-interview (Present State Examination, ICD-10) regarding Schizophrenia and drug dependency by psychiatrists³⁷. All healthy controls were interviewed with the entire PSE interview. All patients were rated with SANS and SAPS (Scale for the Assessment of Negative/Positive Symptoms)^{38, 39}. All subjects were tested for recent drug use using urine samples (testing for amphetamine, benzodiazepines, cannabis, codeine, morphine, cocaine) on the day of the fMRI scan. The neurocognitive testing and measures of psychopathology were done 1-3 days ahead of the fMRI scan.

Animated Triangles Task (ATT)

The ATT^{18, 23} consists of short movie clips with two animated triangles. In the ‘random’ movement condition, the triangles move in an arbitrary way e.g. bouncing. In the ‘intentional’ (ToM) condition, two triangles interact in a socially complex way where one triangle appears, to most observers, to influence the mental state of the other triangle. The behavioral paradigm consisted of 8 animation clips, 4 of each condition lasting 38-41 seconds each. After each clip, the subjects were asked to tell what they thought was happening in the clips. Answers were recorded and transcribed. Two clinical psychologists, who were blinded to the subjects’ group status, evaluated each answer and mean scores were calculated for each subject. The subjects’ answers were scored regarding intentionality (degree of mental state attribution, range 0-5); and accuracy (how accurate was the description, range 0-3) as outlined by Castelli et al.¹⁸. Inter-rater agreement was moderate to almost perfect (intentionality for random animations: $\kappa = 0.72$, $Z = 4.82$, $P < 0.0001$; intentionality for ToM animations: $\kappa = 0.85$, $Z = 9.69$, $P < 0.0001$; accuracy for random animations: $\kappa = 0.66$, $Z = 5.77$, $P < 0.0001$; accuracy for ToM animations: $\kappa = 0.51$, $Z = 7.37$, $P < 0.0001$) (Figure 1)

Behavioural data analysis

Statistical analysis was done with Stata IC 14 (64-bit) software. Patients with first-episode schizophrenia and controls (N = 17 pairs) were compared with regard to demographics, psychopathology, IQ and social cognition. Continuous variables were examined by Wilcoxon rank-sum test

(Mann-Whitney) and reported with mean and 95 % confidence intervals. Effect sizes of the continuous variables were reported by Harrell's C and 95 % confidence intervals. Harrell's C is a rank parameter measuring the ordinal predictive power of a model. Categorical variables were examined by Fisher's exact test and reported with the counts and proportions of the total group in percentages. The social cognitive data was further analyzed by linear regression using current IQ as a co-variate.

MRI acquisition

MRI imaging used a Siemens Magnetom Tim Trio scanner with a 16 channel head coil (Erlangen, Germany) at the Danish Neuroscience Centre. 176 slice whole brain T1 weighted images (265x256, 1 mm voxels, TE 2.52 ms TR 1900 ms) were obtained for anatomical registration of functional scans. Functional data was collected as T2-weighted echo planar images (EPI) in an interleaved slice acquisition order. Each volume (96 * 96 matrix, 2 mm voxels; TE, 27 ms; TR, 3300 ms) contained 61 slices.

Image Preprocessing

Preprocessing was carried out with FEAT v. 6.0 from FMRIB's Software Library (FSL) ⁴⁰. Brain matter was segmented from non-brain using a mesh deformation approach ⁴¹. High pass temporal filtering was applied using a Gaussian-weighted running lines filter, with a cut-off of 205s (twice the maximum period between trials of the same type) ⁴². Each volume was motion corrected and smoothed with a Gaussian filter (full-width half- maximum of 5

mm). Independent Component Analysis was used to visually identify and remove obvious artifacts in the data using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) software⁴³.

FMRI Design

Single Subject Analysis

FSL (the FMRIB Software Library) was used to analyze the data⁴⁴. The general linear model contained 4 boxcar regressors for periods during: intentional movement videos, random movement videos, a still picture baseline and question periods (see supplemental material for detail). Regressors were convolved with the default FSL hemodynamic response function (gamma function, delay = 6s, standard deviation = 3s) and filtered by the same high pass filter as the data. Contrasts were set up between the random and ToM movement conditions. Images were linearly registered to T1 structural images and standard MNI space.

Group Analysis

Patients were matched one-to-one with their control in a two-sample paired t-test using a model that included a contrast between groups and additional dummy regressors for each pair of subjects. Patient groups were also analyzed separately. Group-level analysis was carried out with FLAME 1+2⁴⁵ with automatic outlier reduction. The Z statistic maps were cluster corrected (contiguous clusters conservatively defined by voxels with a conservative $Z > 3$) with a whole brain cluster significance level of $P < 0.05$ ⁴⁶⁻⁴⁹. Correlations

between neural responses to ATT conditions and positive / negative symptoms was also investigated (see supplemental material).

3. Results

Demographics, psychopathology, IQ and social cognition

Demographics, psychopathology, IQ and social cognition are summarized in Table 1. As expected FES subjects and healthy controls did not differ in age and gender. In spite of our carefully match based on parental education and social economic class and the last commenced education of the subjects the FES subjects had almost three years less education than the HC's (FES: 12.35 95% CI (11.07;13.64); HC:15.18 95% CI (13.66;16.69), $Z = -0.36$, $P = 0.72$). Ten FES patients were unemployed and 2 on sick leave while all HC's were either students or had a job. This could probably be explained by the fact that the FES subjects on average had experienced psychotic symptoms for several years (mean duration of untreated illness 13.35 95% CI (9.40;17.31) years). These symptoms were e.g. reported as hearing voices since kindergarten. The FES patients had a surprisingly long duration of untreated illness. Responses reflected duration of psychotic or psychotic-like symptoms, mainly auditory hallucinations. Future research may wish to elaborate on this and ask subjects of ultra-high risk criteria or basic symptoms⁵⁰.

FES subjects and HC's did not differ in estimated premorbid IQ (DART: FES 32 95% CI (30.32;33.68), HC 34.35 95% CI (31.56;37.15), $Z = 1.87$, $P = 0.06$). However, they differed in estimated current IQ (WAIS: FES

92.29 95% CI (80.68;103.91), HC 112.47 95% CI (106.19;118.75), $Z = 2.72$, $P = 0.01$).

FES subjects saw less intentionality compared to the HC's in the intentional movement animations (FES: 12.06 95 % CI (9.73;14.39); HC: 15.38 95% CI (14.11;16.65), $Z = 2.18$, $P = 0.03$) which might be due to hypo-mentalizing. Importantly, they also saw more intentionality in the random animations than the HC's which might be due to hyper-mentalizing (FES: 1.32 95 % CI (0.52;2.13); HC: 0.32 95 % CI (-0.04;0.68), $Z = -2.09$, $P = 0.04$) (Figure 2).

Patients' descriptions of animations were less accurate than the HC's both with regard to the intentional movement animations (FES: 6.97 95 % CI (5.77;8.17); HC: 9.29 95 % CI (8.63;9.96), $Z = 2.89$, $P < 0.01$) and the random animations (FES: 10.24 95 % CI (9.16;11.32); HC: 11.82 95 % CI (11.67;11.98), $Z = 2.45$, $P = 0.01$) (Figure 1). However, the above mentioned social cognitive differences did not remain significant when controlling for current IQ (all P s > 0.11). There was an interaction between IQ and subject group (patient or control) in the accuracy score of the random movements, however conditional main effects between groups were non-significant in this model ($\beta = -5.61$, $SE = 3.49$, $t = -1.61$, $P = 0.12$).

fMRI Results

In the control group, intentional (ToM) movement activated greater temporal gyrus, occipital cortex and inferior frontal cortex. Activation overlapped with previous findings of a pSTS response on this contrast^{18, 51}, assuring that the normal response was as expected and modelling of responses was correct.

Qualitatively, patients had a similar pattern. Statistical comparison between groups revealed differences in another region, as described below. See supplemental material for individual group activations.

We focused on the interaction effect of patient (intentional – random) – control (intentional – random) to account for differences of baseline activation during task performance. Using a whole-brain search, this interaction effect was observed only in a region of amPFC (Peak MNI Coordinates (x y z in mm): 6, 62, 16, $Z_{\max} = 4.2$, 138 voxels, $P = 0.01$) (Figure 3). Within this region, t Tests showed that only the patient group showed a clear difference between conditions, with responses to random movement being higher than intentional movement (Figure 2): Patients: Mean difference 16.79 95% CI (4.1;29.5) (arbitrary units (a.u.); $T(16) = 2.8$, $P = 0.013$. Controls: Mean difference: -7.4, 95% CI (-4.08, 18.92) (a.u). $T(16) = -1.4$, $P = 0.19$).

4. Discussion

The behavioural data show that FES patients both hypo-mentalize and hyper-mentalize with neural evidence for the latter. Behaviourally, FES patients were less accurate in their descriptions of triangle actions in both conditions compared to the healthy controls. However, these differences were influenced by group differences in IQ.

In the control group, the contrast of intentional to random movement observation showed a pattern encompassing pSTS activation found in previous studies^{18, 51}. This region did not respond differently in patients.

However, within another region that is historically associated with this contrast¹⁸ and other mentalizing processes⁵², FES patients presented a different pattern to that of controls. Unlike the controls, an amPFC region of patients was more active while studying random movement, compared to studying movement normally described as intentional. Yet, they did not eventually ascribe more intentionality to this (vs the intentional) condition. This points to an association between amPFC and the act or effort of mentalizing, rather than its consequences.

From this perspective, we propose that patients tried to interpret what they saw, as they were instructed, in all situations where there was initially potential for intentionality. They continued to mentalize while observing the random movement, which would be a more prolonged and effortful process than the ‘intentional’ condition (where the intentions were soon apparent). This would result in greater mentalizing-based neural activity. This could be a form of hyper-mentalizing, whereby patients fail to accept the absence of intentionality and turn off mentalizing processes – and instead ramp them up, despite evidence to the contrary. This response may be limited to contexts where intentionality is initially possible, whereby patients fail to change prior expectations when presented with evidence that intention is not present. If this process goes unabated, patients are likely, on more occasions than normal, to interpret non-social events (which might by chance look social), as having intentionality.

As with previous fMRI studies using the ATT^{25-28, 53} we found abnormal activity patterns in the mentalizing network of FES patients compared to healthy controls. However, in contrast to other ATT fMRI studies, our findings

were restricted to dysfunctional activation in amPFC. A possible explanation for this might be that the previous fMRI studies using the ATT differed on key issues. These differences might explain divergent results of former studies, e.g. sample sizes were small ($N = 15-20$), the Das et al. sample comprised solely of male patients^{25, 26} and Koelkebeck investigated a sample from a different culture²⁷

Furthermore, in contrast to previous studies, we examined patients with minimal or no exposure to antipsychotic medication. It is known that antipsychotic medication influences the brain processes in schizophrenia⁵⁴⁻⁵⁶.

Having fewer positive symptoms and more negative symptoms as a patient was associated with neural responses to intentional (in reward associated ventral caudate and lateral frontal pole) and random movements. See supplemental material.

All, but one, of our patients were scanned within 5 days of receiving their diagnosis. At the other end of the scale, the Martin et al. study investigated patients with a duration of the schizophrenia diagnosis of more than 21 years on average²⁸ and twice as old as our sample. A recent meta-analysis showed more comprehensive mentalizing deficits in patients with long lasting schizophrenia compared to FES based on behavioral intentionality data from the ATT¹³

Based on the 10-year follow-up studies of the OPUS FES patients, we also know that patients have very different prognosis, where some patients recover while others remain severely ill^{31, 57-59}. Identification of deficits unique to FES can help us make predictions about the cause of the disorder, the experience of early symptoms, the prognosis of patients, and the changes that occur with

years of ongoing treatment. A direct comparison between chronic patients and FES patients may not be valid given the range of cognitive differences between the two groups¹³ but one can inform the development of the other. Future research, paired with neuroimaging, can be used to further the relationship with longitudinal studies. One might also consider doing meta-analysis based on MRI data from FES patients with sparse exposure to medication in order to investigate functional connectivity of the mentalizing network as per Schillbach et al.²⁰.

FES patients have different ToM deficits (using the ATT) depending on their level of positive and negative symptoms⁹. Our supplemental analysis lends neural support to this finding, which should be further investigated in a larger sample.

Historically, neuroimaging of the ATT has differed between studies. While some studies use an explicit type of responding (asking subjects to answer questions during scanning) other studies use a more implicit type of task administration (merely asking subjects to passively watch the film clips during scanning). Martin et al. mentions how this might explain why some studies find under-activity in the same areas as other studies found over-activity²⁸. The ATT has recently been standardised and included as the social cognitive fMRI paradigm of the Human Connectome Project^{51, 60}. This will help future research achieve more comparable fMRI data.

4.1 Clinical implications of the results

Results imply that FES patients have abnormal mentalizing abilities. Our results suggest the presence of simultaneous hyper-mentalizing and hypo-mentalizing in

patients. This means that a patient can both under-interpret and misunderstand intended social interaction from another human being. At the same time the patient can over-interpret neutral non-interactions. This illustrates the complexity of social cognitive deficits in schizophrenia and results should be implemented in psychosocial interventions. For example, cognitive behavioral therapy tends to focus on the negative automatic thoughts of the patient. Our results imply that it is also crucial for therapy to focus on helping the patient find out in detail who-did-what-to-whom-and-why.

4.2 Limitations

Our study illustrates the challenges of scanning newly diagnosed, unmedicated patients. We had 6 patients who were not able to complete the scans due to worsening of symptoms because of scanner noise, which adds to the challenge of patients wishing to avoid to avoid social interaction with an unfamiliar person. While the NART has been found to be a valid and reliable measure of estimated premorbid intelligence in schizophrenia^{33, 34}, it is possible that premorbid IQ was underestimated due to developmental delays, prodromal symptomatology or early illness onset. While the 4 subtests selected from WAIS-III have been found to be highly correlated with full scale IQ³⁶, they do not capture the same variance as a full WAIS-III assessment. Therefore, matching of participants should be interpreted with some caution and fMRI results not interpreted as independent of the effects of schizophrenia on intelligence scores.

A larger sample size may reveal further neural differences within and between groups.

4.4 Conclusion

Our results imply that FES patients can have simultaneously hyper-mentalizing and hypo-mentalizing tendencies. Neural correlates indicate that patients apply ToM processes despite low-level cues indicating that this would be inappropriate. Duration of illness needs to be taken into consideration when comparing fMRI results in schizophrenia. Results demonstrate the complexity of ToM deficits in schizophrenia and this should be taken into consideration when offering social cognitive training programs.

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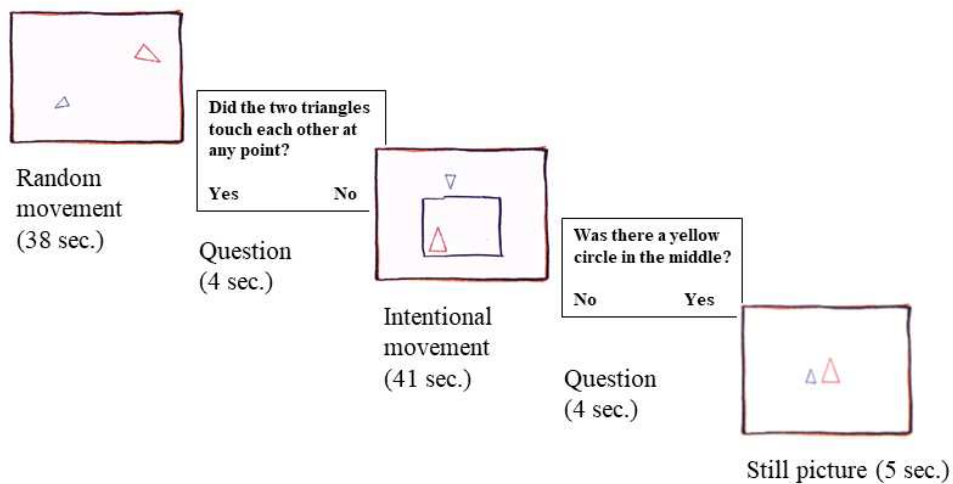
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Table 1 Comparison of patients with First-episode schizophrenia (FES) and controls on demographics, psychopathology, IQ and social cognition. Continuous variables were examined by Wilcoxon rank-sum test (Mann-Whitney) and reported with mean (95% CI) and effect size by terms of Harrell's C (95% CI). Categorical variables were examined by Fisher's exact test and reported with the counts and proportions of group total, N (percentage).

	First-episode schizophrenia (N=17)	Healthy controls (N=17)	Harrell's C	P value
Age	23.94(21.76;26.11)	23.59(21.50-25.68)	0.46(0.25;0.68)	0.72 ^f
Females	5(29.41)	5(29.41)	-	1.00 ^g
Years of education	12.35(11.07;13.64)	15.18(13.66;16.69)	0.77(0.61;0.93)	0.01 ^f
Current occupation				<0.01 ^g
Unemployed	10(58.82)	0	-	-
Work	0	6(35.29)	-	-
Student	5(29.41)	11(64.71)	-	-
Sick leave	2(11.76)	0	-	-
Days of FES-diagnosis	41.41(3;403) ^a	-	-	-
Years of untreated illness	13.35(9.40-17.31)	-	-	-
SANS ^b	9.76(7.02;12.51)	-	-	-
SAPS ^c	14.71(12.63;16.78)	-	-	-
DART (Est pre IQ) ^d	32(30.32;33.68)	34.35(31.56;37.15)	0.69(0.49;0.89)	0.06 ^f
WAIS-III (Est func IQ) ^e	92.29(80.68;103.91)	112.47(106.19;118.75)	0.77(0.60;0.94)	0.01 ^f
Animated Triangles				
Intentionality ToM	12.06(9.73;14.39)	15.38(14.11;16.65)	0.72(0.53;0.90)	0.03 ^f
Intentionality random	1.32(0.52;2.13)	0.32(-0.04;0.68)	0.32(0.15;0.48)	0.04 ^f
Accuracy ToM	6.97(5.77;8.17)	9.29(8.63;9.96)	0.79(0.62;0.96)	<0.01 ^f
Accuracy random	10.24(9.16;11.32)	11.82(11.67;11.98)	0.72(0.55;0.89)	0.01 ^f

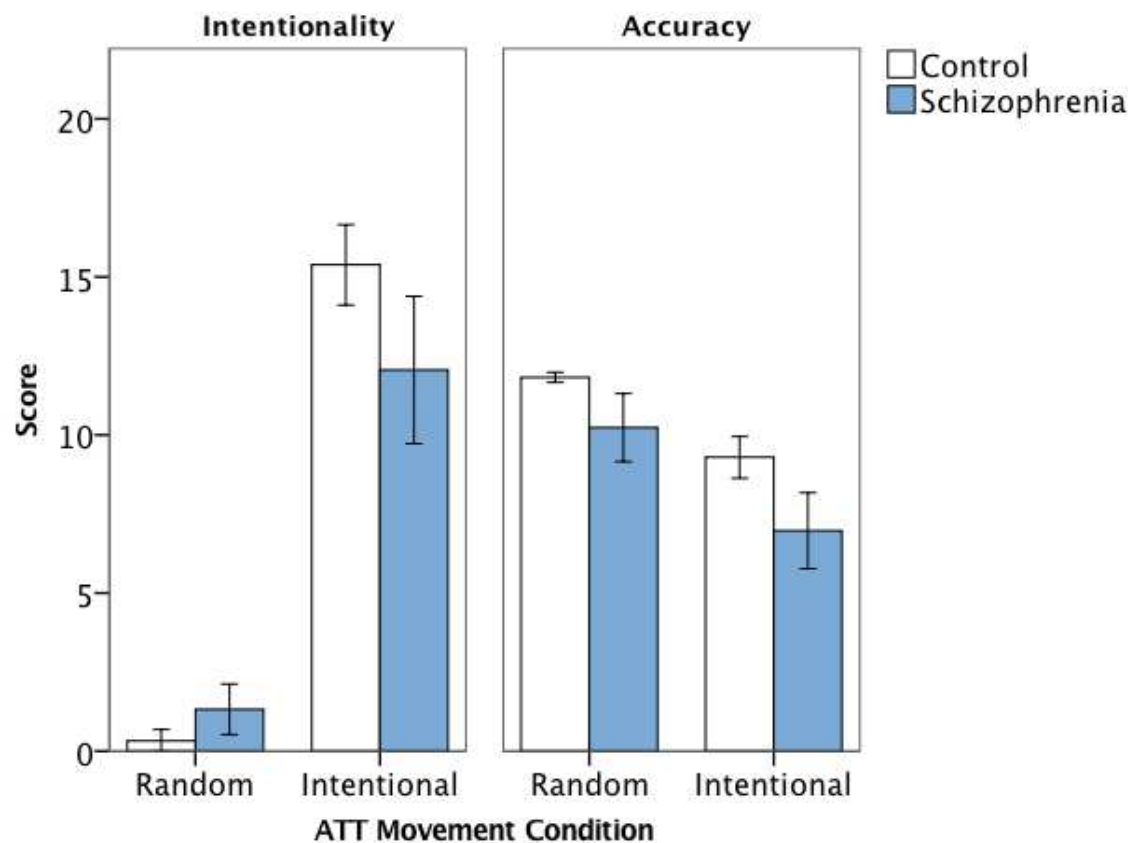
a) Min and max values; b) SANS, Scale for Assessment of Negative Symptoms; c) SAPS, Scale for Assessment of Positive Symptoms; d) DART, Danish Adult Reading Test; e) Wechsler Adult Intelligence Scale-III (Matrix Reasoning, Block Design, Vocabulary, Similarities); f) Mann-Whitney test; g) Fisher's exact test

Figure 1 The Animated Triangles Task (ATT)



The scanning paradigm consisted of 4 blocks. Each block contained a presentation of a random and aToM movement sequence. Each clip lasted from 38 to 41 seconds. In addition, each block contained a still picture of a triangle scene, for 5 seconds. After each animation, subjects were asked a yes-no question (lasting 4 seconds) to ensure subjects paid attention to the task (supplementary material). Subjects pressed a button on a response box to indicate their response. There were no more than 128 seconds between two stimuli of the same type and condition. Stimuli were back projected onto a screen that could be seen by the subject in the scanner by way of a mirror placed above their eyes.

Figure 2. Behavioural data from Animated Triangles Task. Ratings of subject reports on what occurred after watching videos of the ATT (moving shapes with apparent intentionality or random movement). All comparisons of FES patients and controls were significant (P 's <0.04). Error bars are 95% C.I.



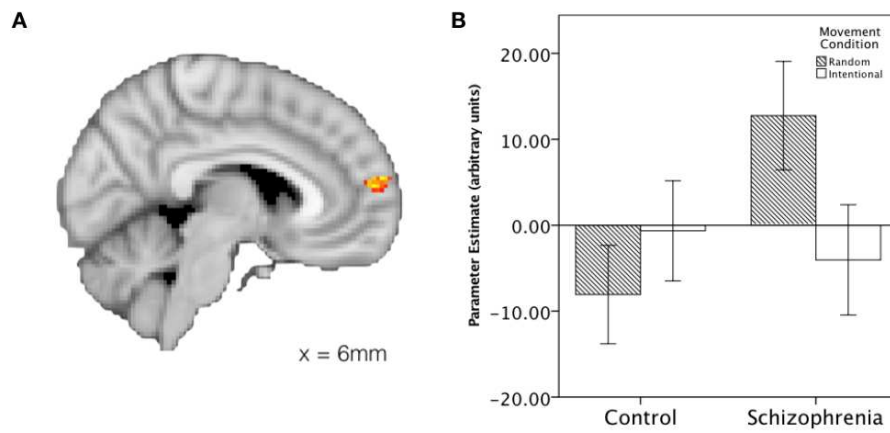


Figure 3. **A.** Activation in the medial prefrontal cortex corresponding to the interaction of patient group and movement condition (thresholded $Z > 3.0$, $P < 0.05$, cluster corrected). Activation overlaid on the MNI152 brain. **B** Within this region of MPFC, centered on the mean beta, the interaction is driven primarily by a greater activation in schizophrenia patients while viewing random movement, confirmed by pair-wise T test. Error bars are within-subject 95% CI.

Hyper- And Hypo-Mentalizing In Patients With First-Episode Schizophrenia: fMRI And Behavioural Studies: Supplementary Material

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Animated Triangles Task (ATT) fMRI paradigm

Table S1. Task Block Design

1. Billiards (38 sec) + Q (4 sec)	2. Surprising (41 sec) + Q (4 sec)	3. Picture 1 (5 sec)
4. Drifting (41 sec) + Q (4 sec)	5. Picture 2 (5 sec)	6. Seducing (36 sec) + Q (4 sec)
7. Picture 3 (5 sec)	8. Tennis (40 sec) + Q (4 sec)	9. Mocking (39 sec) + Q (4 sec)
10. Picture 4 (5 sec)	11. Star (40 sec) + Q (4 sec)	12. Coaxing (39 sec) + Q (4 sec)
	Total time	366 sec/ 6 min 6 sec

Q = question period.

Questions for the fMRI study:

Random animations

Billiard: "Did the two triangles at some point touch each other?" . Correct answer: "No"

Drifting: "Was there a square in the middle?" Correct answer: "Yes"

Star: "Did the two triangles touch the square in the middle?" Correct answer: "Yes"

Tennis: "Did the two triangles move around the square in the middle?" Correct answer: "No"

ToM animations

Coaxing: "Were there two triangles?" Correct answer: "Yes"

Mocking: "Was there a square in the middle?" Correct answer: "No"

Seducing: "Was there a blue square to the left?" Correct answer: "Yes"

Surprising: "Was there a yellow circle in the middle?" Correct answer: "No"

Table S2. Differential Neural Responses on the Animated Triangles Task

Controls: intentional - random							
<i>Cluster</i>	<i>Voxels</i>	<i>P</i>	<i>Z</i>	<i>x</i> (mm)	<i>y</i> (mm)	<i>z</i> (mm)	<i>Anatomy (Harvard Oxford Atlas)</i>
6	5315	0.000	5.59	30	-90	-6	occipital cortex (R) (extends into superior temporal gyrus and temporoparietal junction)
5	3669	0.000	6.35	-40	-90	-2	occipital cortex (L) (as above)
4	834	0.000	4.83	58	30	6	inferior frontal gyrus (R)
3	379	0.000	4.44	52	4	-18	superior temporal gyrus (R)
2	312	0.000	4.37	-52	-2	-18	superior temporal gyrus (L)
1	99	0.031	4.04	-42	8	22	inferior Frontal Gyrus (L)
Controls: random - intentional							
11	5647	0.000	5.87	-6	-94	2	occipital cortex (L)
10	1412	0.000	5.37	-22	-50	70	superior parietal lobule (L)
9	647	0.000	4.63	-44	-8	54	precentral gyrus (L)
8	597	0.000	4.29	-4	40	-2	ventral anterior cingulate gyrus (L)
7	533	0.000	4.49	36	52	4	frontal pole (R)
6	334	0.000	4.34	0	6	38	dorsal anterior cingulate gyrus
5	202	0.000	4.32	-2	-34	26	posterior cingulate gyrus (L)
4	182	0.001	4.21	32	20	6	anterior insular cortex (R)
3	143	0.004	4.25	48	-50	50	angular gyrus (R)
2	126	0.009	4.67	28	-6	60	superior frontal / precentral gyrus (R)
1	93	0.041	4.31	-60	-4	38	precentral gyrus (L)
Patients intentional - random							
3	323	0.000	4.51	50	-54	6	middle temporal gyrus (R)
2	309	0.000	4.34	-26	-98	0	occipital cortex (L)
1	288	0.000	4.07	38	-92	-4	occipital cortex (R)
Patients: random - intentional							
4	5756	0.0000	5.5	10	-94	-2	occipital cortex (R)
3	127	0.0193	4.32	28	-6	42	precentral gyrus (R)
2	118	0.0275	4.14	-16	64	-2	frontal pole (L)
1	115	0.0310	4.45	-12	-58	70	superior parietal lobule (L)
Patients (random - intentional) – Controls (random - intentional)							
1	156	0.0059	4.22	12	48	12	paracingulate gyrus

Relationship of Differential Neural Responses to the Animated Triangles Task to Positive and Negative Symptoms

Correlations of responses to task conditions across subjects with positive and negative symptoms (SANS and SAPS scores mean-centered) were tested by adding mean-centered symptom scores to separate group level fMRI models of patients.

Within the patient group, fewer positive symptoms correlated with a greater response to intentional movements (relative to random movements) in left ventral caudate ((x y z (mm): -6 8 0, Z_{\max} = 4.4, 103 voxels, P = 0.04), a region previously associated with this contrast on the ATT ¹, reward ² and salience³. Though by reverse inference, would tentatively interpret this as reflecting the greater salience or enjoyment of the intentional films when confidently understood. Bilaterally, lateral frontal pole also responded this way: left (-28 46 8, Z_{\max} = 4.6, 235 voxels, P < 0.001) and right (24 46 14, Z_{\max} = 4.7, 188 voxels, P < 0.002). This region has been associated with many forms of higher order cognition, but perhaps most relevant to the ATT is the assessment of relationships between stimuli ⁴. These may be markers of higher social cognition functioning in the presence of fewer positive symptoms.

More negative symptoms correlated with a relatively greater response to intentional movement (compared to random) in anterior frontal pole (-16 42 42, Z_{\max} = 4.8, 206 voxels, P < 0.001) and left middle frontal gyrus (-50 18 38, Z_{\max} = 4.9, 149 voxels, P = 0.007). While it is interesting for future research to have these markers, an interpretation is not straightforward as these responses could be compensatory or reflect greater cognitive effort in these patients.

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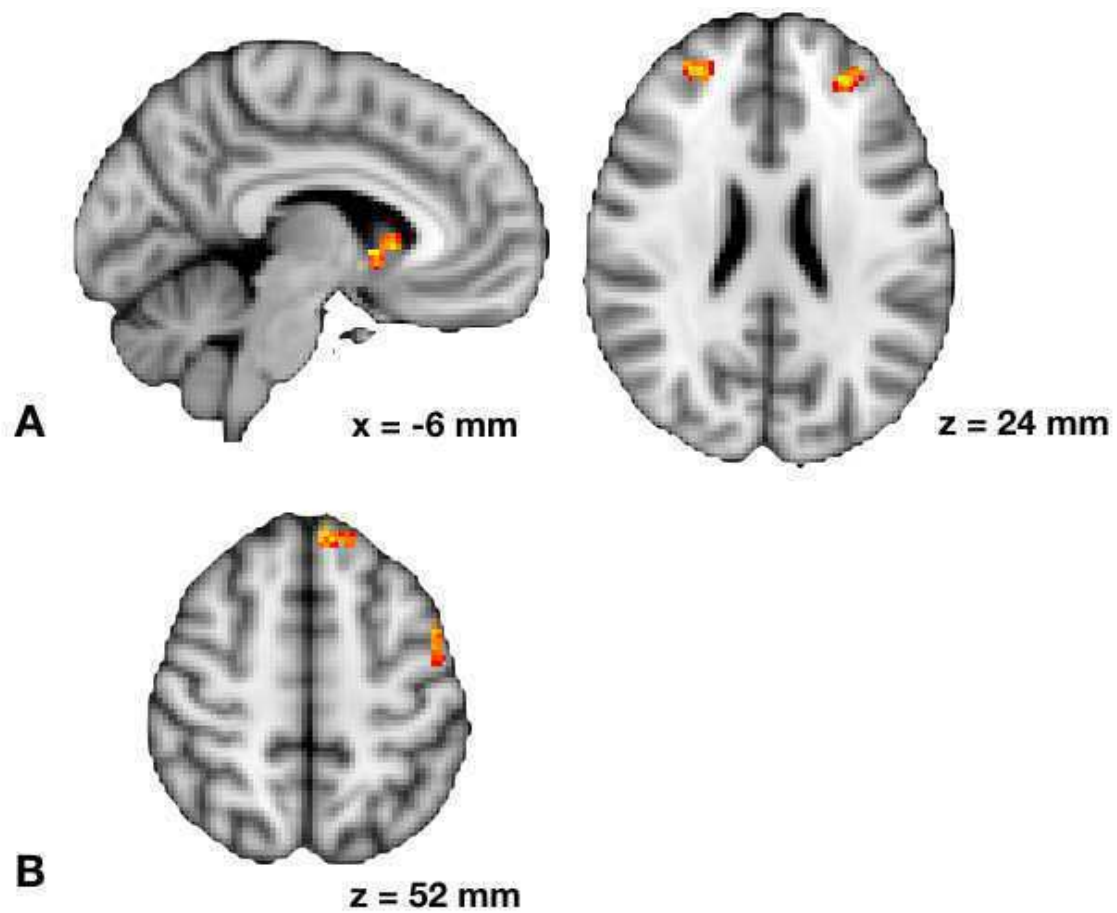


Figure S1. **A.** Increased responses to intentional movements (vs. random) on the ATT with fewer positive symptoms (SAPS) **B.** Increased responses to intentional movements (vs. random) on the ATT with greater negative symptoms (SANS). Both whole brain cluster corrected, using thresholded voxels at $Z > 3.0$, and a cluster significance of $P < 0.05$. Activation overlaid on the MNI152 brain.